Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs

PhRMA

September 8, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0018; Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application; 69 Federal Register 32467; June 10, 2004

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) welcomes the opportunity to comment on the above referenced proposed rule issued by the Food and Drug Administration (FDA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives. Investing more than $32 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

As a general matter, PhRMA supports the FDA's proposal to remove the reference to the Declaration of Helsinki from the Investigational New Drug (IND) regulations. Relying instead on internationally-accepted Good Clinical Practice (GCP) requirements reflects the US-based pharmaceutical industry's adoption of *ICH E6: Consolidated Guideline on Good Clinical Practice* as a global standard for the conduct of sponsored clinical research.

Specific Comments

PhRMA submits the following comments on the proposed changes to FDA regulations at 21 CFR §312.120:

21 CFR §312.120. We request that the International Conference on Harmonization (ICH) standard of GCP be explicitly stated in the Final Rule. This will prevent any ambiguity and give FDA confidence that the standards described in ICH GCP will not change independently of FDA's authority.

21 CFR Part 312.120(a)(2) Although FDA will not accept as support for an IND, NDA or BLA a study that does not meet the conditions of paragraph (a)(i) of this section, FDA will examine data from such a study.

PhRMA requests clarification as to the intent of this section. Does this mean that a sponsor should submit studies conducted on the investigational product but differentiate studies that comply for FDA review of safety and efficacy or that the FDA will review noncompliant studies as supportive?

2004N-0018 C 5

21 CFR 312.120 (3)(b)(3). The specific reference to "hospital records" suggests that FDA could request hospital records instead of a description of medical records maintained by the investigator and associated with a study. This could raise data privacy concerns.

21 CFR 312.120 (3)(b) (6) and (7): The names and qualifications for the members of the independent ethics committee (IEC) that reviewed the study, summary of IEC's decision;

PhRMA proposes that these requirements be modified to either:

- Request a statement from the IEC that it is organized and operates according to ICH GCP and the applicable laws and regulations, which is consistent with ICH E6 Section 5.11.1(b) and from PhRMA companies experience is more likely to be obtained as the release of names of IEC members can conflict with local privacy regulations; or,
- Require that sponsors use ICH E3 as the standard for preparing a clinical study report. The ICH Guidance on Structure and Content of Clinical Study Reports, E3, was intended to allow the compilation of a single core clinical study report acceptable to all regulatory authorities of the ICH regions. The ICH E3 document requires providing the ethics committee information in appendix 16.1.3 in the form of a "List of IEC's or IRB's (plus the name of the committee Chair, if required by the regulatory authority)".

In requiring "the names and qualifications for the members of the IEC that reviewed the study," Section (b)(6) deviates from the ICH format and would thus require industry to utilize different formats for the clinical study reports (CSRs) from IND and non-IND studies as well as different formats for the submission of non-IND studies to FDA and to other countries' authorities.

21 CFR 312.120 (3)(b) (8), (10) and (11): A description of how informed consent was obtained; A description of how the sponsor(s) monitored the study and ensured that the study was carried out consistent with the study protocol, and; A description of how investigators were trained to comply with GCP and to conduct the study in accordance with the written protocol, and copies of written commitments, if any, by the investigators to comply with GCP and the protocol.

PhRMA companies have adopted ICH standards for conducting clinical research globally. Included in these standards is ICH E3 for the structure and content of clinical study reports. PhRMA requests that FDA modify the above regulatory requirements so that it is acceptable to follow the requirements of E3:

- Section 5.3 "Patient Information and Consent". This section requires that the sponsor describe how and when consent was obtained, and the representative written information for the research subject (if any) and the sample informed consent has to be provided in the appendix 16.1.3. Since the sample informed consent form will describe any incentives that may have been provided, this should meet the intent of (b)(8).
- Section 9.6 "Data Quality Assurance". This section requires that the sponsor describe any steps taken at the investigational sites or centrally to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data such as training sessions, monitoring of investigators, use of centralized testing and data audits. Therefore, the intent of (b) (10) and (11) should be covered in the text of this section of the clinical study report.

- Appendices 16.1.1 "Protocol and Amendments". The written investigator commitments required in section (b) (11) are usually included in the investigator signature page of the study protocol. A blank copy of this page is provided with the protocol in ICH CSR appendix 16.1.1. ICH-GCP Section 8.2.2 requires archival of the individual investigators' signature pages in the sponsor's trial master file. It should suffice to only require a description of how the investigator commitment was obtained to comply with GCP and the protocol and eliminate the proposed requirement to provide a detailed description of investigator training.

In summary, we request FDA to confirm that conducting a study in accordance with ICH GCP and reporting and submitting the study according to ICH E3 (clinical study reports) and M4 (common technical document) standards and FDA's corresponding guidance documents satisfies all the requirements of the proposed revised 21 CFR §312.120. In the cases listed above where the individual requirements of section (b) deviate from the ICH standards, we request that the agency consider modifying the requirements to conform to the ICH CSR and CTD standards thus allowing sponsors to prepare and submit IND and non-IND studies according to a single unified standard.

In conclusion, PhRMA would like to reiterate its support for this proposed rule, and we thank you for your consideration of these comments.

Sincerely,

Allen Goldhamer